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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/845,512	04/30/2001	K. Roger Aoki	D2935CON	3427

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EXAMINER	
HAYES, ROBERT CLINTON	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 05/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/845,512	AOKI ET AL.	
	Examiner	Art Unit	
	Robert C. Hayes, Ph.D.	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 March 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14,16,18,19,21,23,25 and 26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14,16,18,19,21,23,25 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date ___.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. The amendment filed 3/1/06 has been entered.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Applicants' arguments filed 3/1/06 have been fully considered but they are not deemed to be persuasive.

4. Claims 14, 16, 18, 19, 21, 23 & 25-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons made of record in Paper No: 20050830, and as follows.

Applicants argue on page 5 of the response that "a spasmodic torticollis is also known as a dystonia". In contrast to Applicants' assertions, "a dystonia" is a generic condition, in which "a spasmodic torticollis" is but one species of a dystonia (e.g., see the extended lists of dystonias on page 5 of the specification). In contrast, the claims are not limited to "a spasmodic torticollis". Thus, Applicants' arguments are not on point, and the claims still constitute new

matter. In regards to the functional limitation of "substantially alleviated" and "able to hold his head and shoulder in a normal position", this functional language is also limited to "a spasmodic torticollis" dystonia, versus dystonias in general, or to cervical dystonia (i.e., as it relates to claims 19 & 25) wherein "head and shoulders" are not reasonably affected in cerevial dystonia; thereby, also still constituting new matter, for the reasons stated above and as previously made of record.

5. Claims 14, 16, 18, 19, 21, 23 & 25-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for the reasons previously made of record for old claims 11 & 13 in Paper NO: 20040624 & 20050830, as follows.

In contrast to Applicants' assertions, and as previously made of record, the recitation of a "to ***substantially*** alleviate a [undefined] symptom..." is indefinite because it remains unclear when to "***substantially*** alleviate", is no longer "*substantially*" alleviating a symptom. Again, the term "to ***substantially*** alleviate a [undefined] symptom..." in claims 14, 19 & new claim 25 is a relative term which render the claims indefinite.

6. Claims 14, 16, 18, 19, 21, 23 & 25-26 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Ludlow et al. (IDS Ref #ac), in view of Simpson et al. (IDS Ref #ag) and Janovic et al. (IDS Ref #ae), for the reasons made of record for in Paper NOs: 20040624, 20041213 & 20050830, and as follows.

Applicants argue on pages 6-8 of the response that "the claims are not obvious", that "1 unit of botulinum toxin (BoNT) type F is not equivalent to 1 unit of BoNT-E", and that "[t]he prior art teaches away from the use of BoNT-E after use of BoNT-A". In contrast to Applicants' assertions, the claims recite "administering up to 1000 units of a botulinum toxin type A", and then "administering up to 300 units of a botulinum type E", or "wherein the amount of botulinum type A is less then 500 units". In contrast, no where in the claims is the recitation "1 unit of botulinum toxin (BoNT) type F" or "1 unit of BoNT-E" to be administered claimed. Nor is the Examiner's rejection based on such an absolute dosage assumption, in contrast to Applicants' assertions. Accordingly, the ranges broadly recited in the claims are reasonably met by the teachings of Ludlow et al., **in view of** Simpson et al. **and** Janovic et al., which is further consistent with that upheld by the court in *Ex parte* Aoki et al., Appeal No. 1997-2367, for the reasons extensively made of record. *In arguendo*, a difference of "nine" fold in efficacy is encompassed within the ranges claimed and the dosages suggested by the teachings of Ludlow et al., **in view of** Simpson et al. **and** Janovic et al., and therefore, remains consistent with that upheld by the court in *Ex parte* Aoki et al., Appeal No. 1997-2367. Accordingly, the Board in *Ex parte* Aoki et al., Appeal No. 1997-2367) itself stated that:

> "We would remind appellants that absolute predictability is not required. For obviousness under 103, all that is required is a reasonable expectation of success. In re O'Farrell, 853 F.2d 894, 904, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988)."

Second, in contrast to Applicants' assertions that the prior art teaches away from the instant rejection, nothing in the prior art teaches "that antibodies to BoNT-A would cross-react with BoNT-E, but not BoNT-F". Each of these toxins are unique, as illustrated by their unique amino acid sequences, which form the basis for cross-reactivity to antibodies, if any exists. In

other words, BoNT-A is not BoNT-E. They are distinct botulinum toxins, as further taught by Simpson et al. below. Thus, Applicants' assertion is mere speculation with no basis in the facts made of record; especially as it relates to the teachings of Schiavo et al., as argued by Applicants. In addition, common functionality to cleaving SNAP-25 is not equivalent to being "physically similar", which clearly misrepresents the state of the art, as it relates to the well known fact that common amino acid sequences alternatively define epitopes that putatively bind common antibodies. Thus, Applicants' arguments remain not on point, and therefore, remain not persuasive.

In summary, Ludlow et al teach the treatment of neuromuscular disorders such as torticollis (i.e., **cervical dystonia**) and oromandibular **dystonia** (movement disorders characterized by muscle spasm/spasmodic activity) by intramuscular injection of botulinum toxin type F after the patients had already been treated with botulinum toxin type A (i.e., with 1/4 of the dose of type A; pg. 350, 1st full *pp*) and had developed neutralizing antibodies to the type A toxin (i.e., as manifested as a reduced response to type A toxin; pages 349-350; as it relates to claims 19 & 25-26). In particular, Ludlow teach individual dosages of "up to 300 units" in Table 1 for the second botulinum (type F) injections (e.g., patient 1: 285 twice + 150 = 720; as it relates to claims 14 & 19). Ludlow also teach treatment of patients with "up to 300 units" of the second botulinum toxin (e.g. 40 units; Table 1; as it relates to claims 14 & 19), which means that 160 units of botulinum toxin type A was previously administered (i.e., as it relates to being "up to 1000/500 units" of type A, as it relates to claims 14, 16, 19 & 21); and "from 80 units to 460 units" of type A, as it relates to claims 16, 18, 21 & 23). However, Ludlow et al do not teach administration of botulinum toxin type E after administration of botulinum toxin type A.

Simpson et al teach that all of the botulinum serotypes A, B, C1, C2, D, E, F and G are produced by the same species of bacterium, and provide a review of their pharmaceutical activities. In particular, all of the botulinum serotypes block acetylcholine release for nerve endings, and each of the serotypes are taught to be "**antigenically distinct**" (e.g., pages 155-156). Therefore, it is reasonable to expect that administration of any of the serotypes would produce the same physiological effect of blocking cholinergic neuronal transmission by "interrupt[ing] transmission at the muscle end organ" (i.e., reduced muscle spasm/twitch/ dystonias; pages 163-164 & 167). Accordingly, because the serotypes differ antigenically, antibodies developed against a first administered serotype would not be expected to block the activity of a second serotype at the cholinergic receptor. This is consistent with the teachings of Ludlow et al, who teach that the advantage of administering a second serotype toxin is to overcome the reduced responsiveness to the first toxin.

Further, consistent with both the teachings of Ludlow et al and Simpson et al, Jankovic et al teach that botulinum toxin is used for the treatment of neuromuscular disorders such as muscle spasm/back spasms, strabismus, comitant and vertical strabismus, lateral rectus palsy, nystagmus, dysthyroid myopathy, writer's cramp, blepharospasm (page 1187, first column); Wilson's disease, tardive **dystonia**, laryngeal **dystonia**, tardive dyskinesia, Parkinson's and limb/foot focal **dystonia**, tremor (pages 1187, second column & 1190, second column; Table 1); tics, segmental myoclonus, spasms due to chronic multiple sclerosis, spasms due to abnormal bladder control in patients with spinal cord injury, anismus (page 1191, second column). Jankovic et al also teach that "blocking"/neutralizing antibodies develop to the toxin, which thereby reasonably cause patients to show to "substantially alleviate a symptom of the dystonia"

to the toxin (page 1189, column 1; as it relates to claims 14, 19 & 25). Jankovic et al then conclude that "[i]t is likely that patients with antibodies against botulinum toxin will respond to injections with other botulinum toxins that are immunologically distinct from type A" (page 1189, column 1).

Thus, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to use Ludlow's methods of administering botulinum toxin type A to treat movement disorders characterized by muscle spasm/dystonia, followed by administration of another botulinum toxin, such as type E as taught by Simpson or Jankovic, in order to continue reducing muscle spasms/dystonia in these patients. It is emphasized that both Simpson et al and Jankovic specifically suggest administration another botulinum serotype toxin after patients become nonresponsive to a first botulinum toxin (i.e., type A). In that Ludlow teach that a reduced response to type A toxin probably is due to development of neutralizing antibodies to the type A toxin, administration after a "loss of clinical responsiveness" in clinical symptoms would be obvious, in order to maintain a positive clinical response for the patient.

7. New claims 25-26 are rejected on the grounds of *res judicata* (MPEP 706.03 (w)), as the issues presented by these claims are the same as those decided by the Board of Appeals and Interferences in a decision dated November 28, 2000 (*Ex parte* Aoki et al., Appeal No. 1997-2367).

As previously made of record in Paper NOs: 20041213 & 20040624, a "spasm" is a "neuromuscular disorder or condition"/ dystonia, which not patently distinct from that previously decided by the Board, in which the same patient population "suffering from a neuromuscular

disorder or condition" is being treated in both the instant application and in *Ex parte* Aoki et al., Appeal No. 1997-2367. For example, claim 25 requires administering botulinum toxin type E "after the patient exhibits a loss of clinical responsiveness" using no specific dosage, which is known to occur "after the patient exhibits... neutralizing antibodies to botulinum toxin A", which has already been decided by the Board. See MPEP 706.03(w).

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Robert Hayes whose telephone number is (571) 272-0885. The examiner can normally be reached on Monday through Thursday, from 9:00 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, can be reached on (571) 272-0867. The fax phone number for this Group is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Robert C. Hayes, Ph.D.
May 1, 2006

ROBERT C. HAYES, PH.D.
PRIMARY EXAMINER